

Why Is the Nasal Route Redefining Systemic and CNS Drug Delivery?

Converging Trends Driving Changes in Nasal Route Medicines

Until about ten years ago nasal drug delivery was primarily associated with the treatment of local conditions such as allergic rhinitis, sinusitis, and nasal congestion. Since then, advances in pharmaceutical sciences, formulation technologies, device engineering, and patient-centric healthcare are redefining therapeutic opportunities in intranasal drug delivery.

A growing number of prescription systemic-acting drugs originally administered in injectable forms have been successfully repurposed and achieved market approval in metered-dose nasal sprays. Innovative clinical stage pharmaceutical companies are focussing on nasal systemic drug delivery as an efficient route of administration for therapies requiring rapid absorption, ease of use, and improved patient experience. By targeting the highly vascularised nasal mucosa, drugs can enter systemic circulation quickly while bypassing gastrointestinal degradation and first-pass hepatic metabolism, offering a compelling alternative to systemic delivery via oral and injectable route. Further advances in nasal delivery are being driven by efforts to target drug delivery to the olfactory zone as the approach underpinning direct nose-to-brain uptake via the olfactory nerve and epithelial pathways. These exploratory drug transportation pathways may enable the development of clinically effective, and more patient-friendly therapies compared with invasive injections.

At Nemera, we see this evolution being driven by several converging trends: the need for non-invasive treatment options, increasing demand for self-administration, and the shift toward healthcare solutions that can be delivered outside traditional clinical settings. This momentum is reflected in market forecasts, with leading intranasal therapies expected to grow at a compound annual growth rate (CAGR) of 14.7% between 2025 and 2030.¹

New Therapeutic Frontiers for Nasal Systemic Drug Delivery

What was once a route dedicated to local

treatments is expanding across multiple therapeutic areas where speed, convenience, and accessibility are critical.

Emergency and Rescue Medicines

Emergency care remains one of the most established applications for nasal systemic drug delivery. Systemic-acting compounds such as naloxone and nalmefene for opioid overdose reversal; epinephrine for acute epileptic seizures and zavegepant and sumatriptan for migraine rescue, have demonstrated the effectiveness of nasal administration in emergency and rescue situations.

The evolution of the nasal naloxone market provides interesting insights into realistic future opportunities in intranasal systemic-acting drug development.

The FDA's approval of Narcan® (naloxone hydrochloride) nasal spray for over-the-counter (OTC) use in March 2023 marked a significant public health milestone. Driven by the urgent need to address the escalating opioid overdose crisis in the United States, where more than 100,000 overdose deaths have been reported annually, largely linked to synthetic opioids such as fentanyl, the decision aimed to expand access to a life-saving treatment capable of rapidly reversing opioid overdoses.² A key factor supporting both the FDA's decision and the subsequent growth of the nasal naloxone market was the inherent usability of the drug-device combination product.

The ready-to-use single dose nasal spray requires no pre-assembly, can be administered quickly without specialised training, and is suitable for use by family members, caregivers, first responders, and bystanders. Based on robust evidence demonstrating the safety of naloxone and the ease with which consumers can correctly use the nasal spray device without healthcare professional supervision, the FDA concluded that OTC availability was appropriate. This combination of clinical effectiveness, accessibility, and user-friendly device design has reinforced the nasal route as a compelling platform for emergency interventions.

Beyond its immediate public health impact, the OTC switch has provided strong

regulatory validation for nasal drug delivery as a route capable of accommodating self-administration in acute critical care situations. The approval has reinforced industry confidence in nasal technologies, encouraging further investment and development across a broader range of therapeutic areas where improved accessibility, emergency intervention, or patient self-management can deliver meaningful healthcare benefits.

Metabolic and Cardiovascular Disorders

For the treatment of severe hypoglycaemia, nasal glucagon was developed primarily to solve a practical problem: injectable glucagon is highly effective pharmacologically, but in a real-life emergency it is often difficult for caregivers to prepare and administer correctly. Clinical studies have shown that nasal glucagon provides comparable glucose recovery while being substantially easier to use.

More recently, the approval of etripamil as an on-demand rescue treatment of Paroxysmal Supraventricular Tachycardia (PSVT) enables patients to self-administer at symptom onset to terminate an episode before requiring emergency intervention and intravenous therapy.

These examples illustrate the potential of the nasal route to create therapeutic value in cardiovascular disease management, enabling patients to manage acute episodes independently and safely, reducing reliance on hospital interventions and supporting the broader trend toward decentralised care.

Neurological and Mental Health Care

The growing burden of mental health disorders, combined with the need for rapid therapeutic intervention, is driving interest in intranasal approaches for central nervous system (CNS)-acting therapies. Among the most notable examples is esketamine nasal spray, approved for treatment-resistant depression and major depressive disorder with acute suicidal ideation or behaviour. Intranasal, esketamine has been shown to provide rapid systemic absorption resulting in clinical benefits and is therefore a viable alternative to traditional oral antidepressant therapies, which may require several weeks to achieve full therapeutic effect.

Beyond depression, pharmaceutical companies are actively exploring intranasal approaches for anxiety disorders, post-traumatic stress disorder (PTSD), schizophrenia, and other neuropsychiatric conditions where rapid symptom control, improved patient adherence, or enhanced CNS exposure may offer clinical benefits. As innovation in formulation science and device technologies continues, mental health care is expected to remain a key area of growth for nasal systemic drug delivery.

Central Nervous System and Brain Diseases

Nose-to-brain delivery continues to attract interest as a non-invasive strategy for transporting therapeutics to the CNS and the brain while potentially circumventing the blood-brain barrier and avoiding undesirable systemic exposure. The therapeutic scope encompasses chronic neurodegenerative conditions, particularly Alzheimer's and Parkinson's diseases and brain tissue damage and primary or metastatic brain cancers.

Therapeutic compounds under investigation range from conventional small molecules to peptides and proteins, including insulin, growth factors and neuropeptides, as well as antibodies, nucleic-acid-based therapeutics and extracellular vesicle-derived biological materials.

However, successful translation will depend not only on the intrinsic properties of the active substance, such as molecular weight, stability, lipophilicity and surface charge, but also on formulation characteristics, nasal anatomy, and delivery-device performance. This is driving research in advanced formulations designed to protect sensitive active ingredients, increase residence time at the nasal mucosa and facilitate transport towards or across the nose-brain interface. Examples include mucoadhesive and thermo-responsive gels, liposomes, polymeric nanoparticles, nanostructured lipid carriers and lipid nanoparticles. Exosomes and other extracellular vesicles are also emerging as biologically derived carriers with potential applications in CNS and brain delivery.

As innovation in pharmaceutical sciences and device design advance in parallel, the N2B route may unlock new therapeutic possibilities for a significant number of high interest compounds that cannot cross the blood-brain barrier.

An Attractive and Fast-Growing Market

Several indicators highlight the growing commercial opportunity for nasal systemic drug delivery:

- Leading intranasal therapies are forecast to grow at a compound annual growth

rate (CAGR) of 14.7% between 2025 and 2030, reflecting sustained investment across both established and emerging therapeutic areas.¹

- The global epinephrine market is projected to exceed \$6 billion by 2033, supported by growing interest in needle-free treatment options and the emergence of novel intranasal alternatives to traditional autoinjectors.³
- The successful commercialisation of products such as Narcan® (naloxone), Baqsimi® (glucagon), Spravato® (esketamine) and Zavprel® (zavegepant) confirms the ability of nasal delivery technologies to support diverse therapeutic applications, ranging from emergency interventions to chronic disease management.

Together, these trends indicate that nasal delivery is evolving from a niche administration route into a strategically important segment of the drug delivery market.

Device Innovation: Enabling the Next Generation of Nasal Systemic Therapies

As nasal delivery expands into new therapeutic frontiers, successful products increasingly rely on delivery systems that combine performance, ease of use, and development flexibility. Nemer's portfolio of nasal platforms, including UniSpray (Figure 1), DuoSpray (Figure 2) and Guided Stream Technology (Figure 3) have been developed to address the evolving needs of systemic, CNS, and nose-to-brain therapies, providing pharmaceutical companies with scalable, patient-centric solutions that support differentiated products across both established and emerging therapeutic areas.

UniSpray: A Unit-Dose Platform for Emergency and Rescue Therapies

UniSpray is a ready-to-use, primeless nasal device designed to deliver a single metered liquid dose of 100 µL through one-handed actuation and in 360° device orientations. After actuation, the plunger is secured in its final position, providing a visible indication that the device has been used, preventing inadvertent reuse and limiting post-use disassembly (Figure 1). It is compliant with the FDA's strict reliability specifications for rescue and emergency medicines.

UniSpray is strategically positioned as a robust platform for both generic and over-the-counter (OTC) naloxone nasal sprays. It has been evaluated against the reference

Life-saving, emergency & crisis application.

KEY POINTS

- **Single metered dose** of 100 µL
- **One-handed activation** & 360° handling
- Compliant with **reliability** criteria for emergency use applications
- Clear activation **confirmation after use**
- **Proven bioequivalence** versus key reference products



Figure 1: UniSpray IPI2



KEY POINTS

- **Two metered doses of 100 µL (200 µL total)**
- **Visual dose indicator**
- **One-handed activation & 360° handling**
- **Compatible with industry-standard filling processes**
- **Supports in vitro bioequivalence strategies**

Figure 2: DuoSpray

product Narcan® through a comprehensive test programme including usability, threshold and interchangeability assessments. These studies demonstrated that users can operate the device safely, reliably and without training, supporting the demands of real-world overdose situations. Importantly, the FDA-reviewed threshold analysis concluded that the identified design differences between UniSpray and the reference product did not affect critical user interactions, dose delivery, activation or overall performance. Furthermore, the subsequent interchangeability assessment confirmed that individuals familiar with Narcan® could transition to UniSpray without additional training. Based on these findings, the FDA determined that no comparative human factors study was necessary, reinforcing UniSpray's suitability as a regulatory-ready platform that can help accelerate the development of affordable generic and OTC naloxone products.

Leveraging Nemera's proven experience in emergency and rescue therapies, this is a regulatory-ready platform supported by bioequivalence data generated in generic development programmes for epinephrine, nalmeferine and zavegepant, helping accelerate development timelines and reduce programme risk.

DuoSpray: Precision for Acute and Rescue Therapies

For therapies requiring accurate bidose administration, DuoSpray provides a ready-to-use solution featuring:

- Two metered sprays of 100 µL each
- No priming required before use
- User-friendly administration in time-critical situations

These characteristics make DuoSpray particularly well suited for acute and rescue applications, including cardiovascular and neurological indications.

Designed to deliver two sequential doses from a single device, DuoSpray supports treatment regimens that may require dose repetition while maintaining a simple and intuitive administration process. The compact, ready-to-use format eliminates preparation steps and enables rapid treatment initiation when speed and ease of use are essential.

The platform combines patient convenience with dosing flexibility, offering pharmaceutical developers a solution adapted to therapies where a second administration may be required to achieve the desired clinical outcome. Its ergonomic design supports use

by patients and caregivers across a range of care settings, from home-based treatment to healthcare environments.

Compatible with established primary container formats and conventional filling processes, DuoSpray facilitates integration into existing pharmaceutical development and manufacturing pathways. This compatibility can help streamline product development while reducing technical complexity during scale-up and commercialisation.

Guided Stream Technology: Designed for Nose-to-Brain Delivery

Realising the clinical potential of CNS and brain-acting therapeutics requires a non-invasive device capable of depositing a defined liquid volume reproducibly in the olfactory region, a small and anatomically remote area located towards the back of the nasal cavity. Conventional atomised nasal sprays were developed primarily for local or systemic delivery and typically deposit most of the emitted dose in the anterior and inferior nasal passages, with reported olfactory deposition generally below 5%.

Nemera is closing this performance gap with its Guided Stream Technology (GST), which combines an established nasal pump with a proprietary nozzle that generates a narrow, directionally stable liquid stream rather than a dispersed atomised plume. The stream is designed to travel up the septal surface into the olfactory cleft. In an anatomically averaged human nasal cast (Figure 4), GST can deliver over 90% of the administered formulation to the defined olfactory region under controlled *in vitro* conditions.⁶ Formulation deposition performance is maintained across a practical range of device orientations, and the impaction force is comparable with marketed pressurised nasal saline products.^{4,5} Collectively, these findings establish GST as a clinically viable, non-invasive platform ready to progress into R&D and human studies to further knowledge in this field.

Conclusion

Nasal systemic drug delivery is evolving into a major growth segment of the pharmaceutical industry, driven by strong clinical and commercial momentum across emergency and rescue medicines, metabolic and cardiovascular disorders, mental health, and CNS-targeted therapies. As pharmaceutical innovators increasingly seek rapid, non-invasive, and patient-friendly treatment options, device performance and usability are becoming critical determinants of success.



KEY POINTS

- **High olfactory deposition** for targeted CNS delivery
- **Directionally stable liquid stream** technology
- **Robust performance** in simulated clinical settings
- Ready to support **next-generation CNS therapeutics**

Figure 3: Guided Stream Technology

Through platforms such as UniSpray, DuoSpray, and Guided Stream Technology, Nemera is enabling the next generation of nasal therapies by combining robust delivery performance, regulatory readiness, and patient-centric design to support improved treatment access, adherence, and outcomes.

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Figure 4 – Nemera CUBO nasal cast showing delivery of a coloured liquid formulation to the representative olfactory zone using the GST device with an automatic actuation, in a controlled experimental setting

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